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Intrathecal Chemotherapy Post Hematopoietic Cell Transplantation for Prevention of Central Nervous System Relapse in Pediatric Acute Leukemia

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Intrathecal (IT) chemotherapy can be given to patients with acute leukemia post hematopoietic stem cell transplant (HSCT) in an attempt to prevent relapse in the central nervous system (CNS). We performed a retrospective analysis of 166 patients with acute leukemia who underwent first HSCT at Memorial Sloan-Kettering Cancer Center between 1999 and 2013. Patients who were not eligible for post HSCT IT prophylaxis due to graft-versus-host disease or acute transplant related complications were excluded from the analysis. Indication for HSCT included acute lymphoblastic leukemia (ALL) (n=115), acute myeloid leukemia (n=45) or acute biphenotypic leukemia (n=6). The median age of patients was 10.7 years (range 0.6-27.5). Disease status at transplant included CR1 (38%), CR2 (44%) and not in remission (4%). Donor grafts underwent ex vivo T cell depletion in 67% (110) of patients, and 71.6% (116) of patients received their graft from an unrelated donor. Conditioning therapy included TBI in 76% of cases. Patients with a history of CNS disease (36%) were included in this analysis; these patients received CNS radiation either during induction therapy or as a boost prior HSCT. Monthly post-transplant IT prophylaxis was administered to 71% of patients, starting at 2 months post HSCT. Prophylaxis consisted of IT cytarabine +/- hydrocortisone, with patients with no prior CNS disease receiving 5 doses post HSCT and those with previous CNS disease receiving 11 doses. The rate of overall relapse at 2 years was 33.2% for the entire cohort, with a CNS relapse rate of 5.4%. The CNS relapse rate at 2 years for patients with ALL was 7.1%, and only 1 patient with AML developed CNS relapse. In subset analysis, patients with ALL who received IT prophylaxis post HSCT had a significantly lower rate of CNS relapse compared to those that did not (4.4% vs 17.3%, P = 0.04). Our study demonstrates that monthly IT prophylaxis with cytarabine +/- hydrocortisone post HSCT may be beneficial for patients with acute lymphoblastic leukemia in the prevention of CNS relapse.

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Mixed Chimerism and Graft Loss in Pediatric Recipients of an Alemtuzumab-Based Reduced-Intensity Conditioning Regimen for Nonmalignant Disease

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Reduced-intensity conditioning (RIC) regimens are increasingly used to reduce transplant-related mortality (TRM) for pediatric patients (pts) undergoing hematopoietic cell transplantation (HCT) for nonmalignant diseases. However, these pts are at increased risk for post-transplant mixed donor/recipient chimerism (MC) and/or primary and secondary graft failure (GF). Intervention with donor lymphocytes (DLI) or second transplants may be necessary, but there is limited information about timing and results of intervention. We retrospectively evaluated 31 consecutive pediatric recipients of an alemtuzumab-based RIC HCT at the Children's Hospital of Philadelphia from May 2007 to December 2012 to determine the incidence of MC and GF, and timing of interventions. All pts received alemtuzumab (Campath) with either fludarabine (150mg/m^2)/melphalan (140 mg/m^2) (n=30) or fludarabine/busulfan (n=1). The timing of Campath differed according to disease. Pts with hematologic disorders and IPEX received Campath beginning day -21 or -22. Pts with hemophagocytic lymphohistiocytosis (HLH) received proximal (N=8) or intermediate (n=2) Campath starting at day -9 or -13, respectively. Diagnoses included HLH in 10 pts, hemoglobinopathy in 8 pts, primary immunodeficiency in 8 pts, and bone marrow failure in 5 pts. All grafts were unmanipulated bone marrow from matched sibling donors (45%), matched unrelated donors (52%) or mismatched related donor (3%). Donor chimerism was evaluated using polymerase chain reaction of microsatellite markers/short tandem repeats at regular intervals post-transplant. Four pts died of TRM (n=3) or early disease progression (n=1) and were not included in the analysis. Of the 27 surviving pts, 18 (66.7%) displayed MC (donor chimerism <100%) on at least one occasion, with 12 (44.4%) reaching a nadir MC level <80%. Two pts with MC≥80% experienced recurrent disease, one with HLH and one with auto-immune syndrome. Of the 12 pts with nadir MC<80%, 6 received DLI with 2 subsequent GFs. Of the remaining 6 pts who did not receive DLI, there were also 2 GFs. The overall incidence of GF/recurrence was 22.2% (6/27). Within the HLH group 7/7 surviving pts developed MC, with 5 (71.4%) reaching a nadir <80%. Despite DLI/boost in all 5 of these pts, 2 progressed to GF. The incidence of GF/recurrence in the surviving HLH pts was 42.9% (3/7) By contrast, in the non-HLH pts, only 11 of 20 (55.0%) surviving pts developed MC with 7 (35.0%) reaching a nadir<80%. Of these 7 with MC<80%, 2 progressed to GF for an overall incidence of GF/recurrence of disease of 15% (3/20). In summary, we observed a high incidence of MC and GF in recipients of Campath-based RIC, particularly in HLH pts. The role for DLI/boost in preventing GF in pts receiving RIC HCT for non-malignant disease who experience low/falling MC requires further study.

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Incidence of and Risk Factors for Cytomegalovirus (CMV), Epstein Barr Virus (EBV) and Adenovirus (ADV) Reactivation in Pediatric Recipients Post Allogeneic Hematopoietic Stem Cell Transplantation (AlloHCT)

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Viral infections are associated with significant morbidity and mortality following AlloHCT. There are no established guidelines for the frequency of viral monitoring and only a few studies in children have analyzed the impact of viremia on AlloHCT related outcomes. In 2008, our center created a standard operating procedure of prospective PCR monitoring for CMV, EBV and ADV prior to AlloHCT and then weekly for 180 days post AlloHCT.

Patients were considered to have viral reactivation if CMV, EBV and ADV copies/ml were ≥600, 1000 and 1000, respectively. Viremia was defined as peri-AlloHCT (d0 - d+14), early viremia (d15 - d+98) and late viremia (d+99 - d+180). From 2008- 2012, 100 consecutive children (median age, 8 yrs; range 0.25-22 yrs; 35F/ 65M) undergoing AlloHSCT for malignant (n=53) and nonmalignant (n=47) disorders, were monitored. Donor sources included: matched family donor (n= 42, 42%), matched unrelated donors (n=28, 28%) and unrelated cord bloods (n=20, 20%). Patients were conditioned with either myeloablative [MA] (n=43, 43%), reduced toxicity [RT] (n=35, 35%), or reduced intensity [RI] (n=22, 22%) regimens. Additionally, a total of 79 patients (79%) received serotherapy with alemtuzumab (n=48, 48%) or rabbit-Anti-thymocyte globulin [r-ATG] (n=31, 31%).

The incidence of pre-AlloHCT viremia was 8%. The incidence of post-AlloHCT single viremia, multiple viremia and viral disease was 41, 15 and 22% respectively. The incidence of peri-AlloHCT, early and late viremia was CMV: 5%, 22.2% and 6.6%; EBV: 1%, 9.1% and 1.1%; ADV: 5%, 10.1%, and 6.6%, respectively. Viremia was noted in 36/80 (45%) of patients who received serotherapy vs. 5/20 (25%) who did not receive serotherapy (Chi-square test p=0.1). Days for neutrophil, platelet engraftment, incidence of graft failure and aGVHD were not statistically significant between patients with and without viremia.

We performed univariate and multivariate analysis for risk factors associated with viremia: age, sex, donor, stem cell source, graft failure, CMV risk status, alemtuzumab, r-ATG, malignant vs. non-malignant disease, MA vs. RT vs. RI regimens, absolute neutrophil and lymphocyte count at day +30. Only CMV risk status (p=.0002) and pre-AlloHCT viremia (p=0.0095) were significant on multivariate analysis. Among patients with viremia vs. those without viremia, 1yr transplant related mortality (TRM) and all-cause mortality was 23.7% vs. 16.7 (p=.4) and 36.8% vs. 18.5% (p=0.04), respectively.

Among patients with viremia vs. without viremia, the median length of initial hospitalization (LOH) vs. LOH in the first 180 days were 44 days (9-144) vs. 35(19-180) (p=0.02) and 91 days (9-165) vs. 59 days (19-180), (p=0.05) respectively. Post-AlloHSCT viremia remains a significant problem and results in a significantly longer LOH. Potentially due to weekly monitoring the TRM was not significantly higher in patients with viremia.

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Sequential Myeloablative Autologous Stem Cell Transplantation and Reduced Intensity Allogeneic Stem Cell Transplantation in Children, Adolescents and Young Adults with Poor Risk Refractory or Recurrent Hodgkin (HL) and Non-Hodgkin Lymphoma (NHL)

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The outcome of newly diagnosed children, adolescents and young adults (CAYA) with lymphoma has improved significantly over the past 30 years. However, for patients with poor-risk recurrent/refractory lymphoma, outcomes are still dismal (<30%) despite intensive salvage therapy with myeloablative conditioning and autologous stem cell transplantation (MAC AutoSCT) [Bradley/ Cairo, et al. BMT, 2008]. To address this problem, we designed a stem cell transplantation approach to maximize an allogeneic graft versus lymphoma effect in the setting of low disease burden (Cairo et al. BBMT, 2013). We conducted a multi-center prospective study of MAC-AutoSCT, followed by a reduced intensity conditioning and allogeneic hematopoietic stem cell transplant (RIC-AlloHSCT) in selected poor-risk CAYA, with refractory or recurrent HL and NHL. Eligible patients with HD had primary induction failure, early relapse (<12 months off therapy, excluding patients with no prior therapy or radiation only), or late relapse (>12 months off therapy, limited to patients with stage III/IV disease and/or B symptoms at relapse). Eligible patients with NHL had primary induction failure or were in first, second, or third relapse. Conditioning for MAC-AutoSCT consisted of carmustine/etoposide/cyclophosphamide (Harris/Cairo et al. BBMT, 2011). The RIC regimen prior to AlloHSCT consisted of busulfan/fludarabine (Satwani/Cairo et al. BBMT, 2013). Thirty patients (16 HL and 14 NHL), median age of 16yrs and median follow-up of 5yrs, were entered on study. Twenty three patients completed both MAC-AutoSCT and RIC-AlloHSCT. Allogeneic sources included unrelated cord blood (n=9), unrelated donor (n=8) and matched sibling donor (n=6). Following RIC-AlloHSCT (n=23), the incidence of grade II-IV aGvHD was 21.74% and the probability of cGvHD was 13%. The incidence of transplant related mortality following RIC-AlloHSCT was 12%. The 10 year event free survival (EFS) following sequential MAC-AutoSCT and RIC-AlloHSCT (n=23) was 64.0% (95% CI: 46.7%-87.7%); EFS for patients with HL and NHL was 59.8% (95% CI: 37.8%-94.7%) and 70% (95%CI: 46.7%-100%) (p=0.613), respectively. Comparing primary refractory and relapsed lymphoma patients undergoing tandem transplant, the 10 year EFS for patients with refractory disease vs. relapse with stage III-IV disease vs. relapse with stage II disease was 71% vs. 60% vs. 66%, respectively. In summary, this novel approach of MAC-AutoSCT followed by RIC-AlloHSCT in CAYA patients with poor risk lymphoma is feasible and safe. The long-term EFS with this approach is encouraging considering the poor-risk patient characteristics and the use of unrelated donors for RIC-AlloHSCT in the majority of cases.

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Quantitative Monitoring of Minimal Residual Disease after Allogeneic Stem Cell Transplantation in Relapsed Childhood ALL Allows the Identification of Impending Relapse – Results of the ALL BFM SCT 2003 Trial

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